FORM PTO-1390 (REV 10-95) | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | ATTORNEY'S DOCKET NUMBER: AKA 269

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U.S. APPLICATION NO. (If known, see 37 CFR §1.5): 09/787612

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP99/05153	20 SEPTEMBER 1999	21 SEPTEMBER 1998

TITLE OF INVENTION

ORAL DRUG DELIVERY SYSTEM FOR ENHANCING THE BIOAVAILABILITY OF ACTIVE FORM OF GLYCYRRHIZIN

APPLICANT(S) FOR DO/EO/US

TAKADA, Kanji

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ■ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR §1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
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17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):

		CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO	$860.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482)	$690.00	
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))	$710.00	
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO	$1000.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	5 - 20 =	0	x $ 18.00	$0.00	
Independent claims	1 - 3 =	0	x $ 80.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 270.00		
TOTAL OF ABOVE CALCULATIONS =				$860.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28).					
SUBTOTAL =				$860.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =				$860.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =				$860.00	
				Amount to be refunded:	
				charged:	

a. ■ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Customer Number 23,599

PATENT TRADEMARK OFFICE

23599

Filed: 20 MARCH 2001

HBS:kms

SIGNATURE

Harry B. Shubin

NAME

32,004

REGISTRATION NUMBER

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/JP99/05153
International Filing Date	:	20 SEPTEMBER 1999
Priority Date(s) Claimed	:	21 SEPTEMBER 1998
Applicant(s) (DO/EO/US)	:	TAKADA, Kanji

Title: ORAL DRUG DELIVERY SYSTEM FOR ENHANCING THE BIOAVAILABILITY OF ACTIVE FORM OF GLYCYRRHIZIN

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

Please cancel claims 1-9.

Please add new claims 10-14 as follows:

--10. A device for colon-targeted oral delivery of glycyrrhizin comprising a suppository-like shaped article containing an amount of glycyrrhizin, said shaped article being made of a suppository base that melts or liquefies at the body temperature, and a coating film of ethylcellulose enclosing said shaped article and having such a film thickness that when the device is transported through the digestive tract to the colon, the film enclosing the liquefied suppository-like article ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine.

11. The device according to claim 10 wherein said amount of glycyrrhizin is sufficient to overwhelm the rate of hydrolysis thereof by the intestinal flora.

12. The device according to claim 10 wherein said coating film is formed by dipping the shaped article in a solution of ethylcellulose.

13. The device according to claim 13 wherein said shaped article is dusted with a dusting powder to prevent from sticking before dipping.

14. The device according to claim 10 wherein said shaped article further contains an adsorption promoter for glycyrrhizin.--

REMARKS

Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Respectfully submitted,

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HBS:jmm

VERIFICATION OF A TRANSLATION

I, the below named translator, hereby declare that:

My name and post office address are as stated below;

That I am knowledgeable in the English language and in the language in which the below identified international application was filed, and that I believe the English translation of the international application No. PCT/JP99/05153 is a true and complete translation of the above identified international application as filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Date

March 8, 2001

Full name of the translator Michio Akaoka

Signature of the translator M. Akaoka

Post Office Address 1-13 Awajimachi 2-chome, Chuo-ku,
Osaka, 541-0047, Japan

ORAL DRUG DELIVERY SYSTEM FOR ENHANCING THE BIOAVAILABILITY OF ACTIVE FORM OF GLYCYRRHIZIN

[0001]

The present invention relates to a drug delivery system for oral administration of glycyrrhizin. More particularly, it relates to such a drug delivery system for enhancing the bioavailability of glycyrrhizin.

[0002]

Glycyrrhizin is a naturally occurring substance found in licorice root (*Glycyrrhiza glabra L.*) that has long been used as a Chinese medicine. It has a strong sweet taste and is used as a sweetener. In addition, glycyrrhizin is used in the treatment of chronic hepatitis, allergic disorder and other pathological conditions by its intravenous administration.

[0003]

Chemically glycyrrhizin is a glucuronide of glycyrrhetic acid with two moles of glucuronic acid. Several studies on the pharmacokinetic behavior of glycyrrhizin in human and animals have revealed that glycyrrhizin is scarcely detectable in the blood following oral administration but its hydrolyzed product, glycyrrhetic acid, is detectable in the blood. See, Wang, Z. *et al.,* Biol. Pharm. Bull. 17(10):1390-1403(1994); Yamamura, Y. *et al., ibid.,*

18(2):337-341(1995); and Takeda, S. *et al.,* J. Pharm. Pharmacol. 48:902-905(1996). Accordingly, it has been considered that glycyrrhizin is poorly absorbable from digestive tract as such (active form), and hydrolyzed in the digestive tract into glycyrrhetic acid which is known to have only little therapeutic effect on hepatitis. Since glycyrrhizin is mainly absorbed in this form, its bioavailability is very low.

[0004]

In order to enhance the bioavailability, rectal administration of glycyrrhizin in the form of a rectal suppository was proposes (JP-A-01294619, JP-A-03002122 and JP-A-03123731). Other attempts to enhance absorbability from digestive tract include providing an enteric oral preparation containing a fatty acid glyceride (JP-A-03255037) and an oral preparation containing a lipid emulsion or lipid complex (JP-A-06192107). With these prior art suppository and oral preparations, however, the blood concentration of glycyrrhizin does not reach a level sufficient to exhibit its therapeutic effect.

[0005]

There exists, therefore, a need for a method and device for enhancing the bioavailability of active glycyrrhizin in oral route to a therapeutically effective level.

[0006]

SUMMARY OF THE INVENTION

According to the present invention, the above need may be met by providing a colon-targeted oral drug delivery system comprising an amount of glycyrrhizin capable of selectively releasing the same in the colon at a concentration overwhelming the rate of hydrolysis by the intestinal flora. Preferably, all or a portion of the carrier consists of an absorption promoter to promote the absorption of glycyrrhizin released from the drug delivery system.

[0007]

When glycyrrhizin is formulated into such drug delivery systems (DDS), it is released selectively in the colon at such a high concentration that saturates and overwhelms the rate of hydrolysis by the intestinal flora and, therefore, the majority of glycyrrhizin may be absorbed in the active form from the colon to achieve remarkably improved bioavailability.

[0008]

DETAILED DESCRIPTION OF THE INVENTION

The drug delivery system according to the present invention basically comprises a core portion containing glycyrrhizin in admixture with a pharmaceutically acceptable carrier and a skin or shell portion enclosing the core portion. The core portion may take the form of powders, granules, tablets, pills, supporsitories or liquid

preparations. Glycyrrihizin is released and absorbed selectively in the colon upon rupture or disintegration of the skin or shell portion in the colon.

[0009]

The core portion contains glycyrrhizin in an amount sufficient to compensate for and substantially overwhelm the rate of hydrolysis of glycyrrhizin by the intestinal flora.

[0010]

The term "glycyrrhizin" as used herein includes free glycyrrhizin and a salt thereof such as sodium, potassium or ammonium salt.

[0011]

Preferably all or a portion of the carrier consists of a substance that promotes the absorption of glycyrrhizin. Examples of such absorption promoters include a pharmaceutically acceptable organic acid such as citric, malic, maleic, fumaric or tartaric acid; a surfactant such as sodium lauryl sulfate, polyoxyethylene sorbitan, polyoxyethylene hydrogenated castor oil, polyoxyethylene alkyl ether, polyoxyethylene alkylphenyl ether, deoxycholate or ursodeoxycholate; or a chelating agent such as EDTA.

[0012]

The core portion may be produced by a method similar to those methods well known in the art for preparing oral solid preparations. It has been known in the art that the

transit time of unit dosage forms for oral administration through the small intestine after expulsion from the stomach and before arrival at the large intestine (small intestine-transit time) is at around 3-4 hours whereas the time required for expulsion of such dosage forms from the stomach after administration may vary to a large extent. It is also known that a distinct rise in pH in the digestive tracts from around 1-3 in the stomach to around 6-7 in the small intestine. The colon-targeting DDS according to the present invention may be designed on the basis of these known physiological phenomenon. Now the colon-targeting DDS of the present invention will be described in detail.

[0013]

1. Unit dosage forms similar to rectal suppositories encapsulated in anionic polymer capsules

[0014]

As noted above, the transit time of solid unit dosage forms such as tablets or capsules through the small intestine is relatively constant at around 3-4 hours. Accordingly, the anionic polymer capsules are designed to have a wall thickness to be dissolved out within the small intestine-transit time to allow the disintegration of the core portion in the lower part of the small intestine for releasing the drug. The wall thickness may routinely be determined empirically through a series of *in vitro* test.

[0015]

Examples of commercially available anionic (enteric) polymers from which the capsule is made include Eudrgid™ S-100 (methacryl acid-methyl methacrylate copolymer), Eudragit™ anionic polymer 4135F (methacrylic acid-methyl acrylate-methyl methacrylate copolymer) and the like.

[0016]

Since glycylrrhizin must be released in the large intestine at higher concentrations as noted above, unit dosage forms similar to rectal suppositories are well suited as a capsule content for this purpose. The method for preparing such unit dosage forms is well known in the art and comprises the steps of adding glycyrrhizin to a suitable suppository base such as Witepsol™ H15 (higher fatty acid di- and triglycerides available from Dynamit Nobel) while being in molten state to make a suspension, casting the suspension into a mold and then cooling the mold to solidify the suspension. The resulting suppository-like dosage forms are placed in the above-mentioned capsules and the capsule seams are sealed with an adhesive of the same anionic polymer. Alternatively, the suppository-like dosage forms may be encapsulated by forming a coating film of the anionic polymer on the surfaces thereof by the dipping method.

[0017]

2. Time controlled capsule preparations which have an

enteric coating and release the drug in time corresponding to the small intestine transit time after expulsion from the stomach

[0018]

The capsules of this type are known as "colon targeted delivery capsule (CTDC)". See, e.g., Takahashi, Journal of Medicine, Vol. 34, S-1, 237-242 (1998). The pharmaceutical feature of CTDC resides in the fact that a drug is present in a conventional gelatin hard capsule together with a pH adjusting organic acid and the capsule has a multi-layer coating consisting of gastric juice-soluble film layer, water soluble film layer and enteric coating layer. Coated capsule preparations designed for releasing the drug in the lower part of digestive tract disclosed in JP-A-09087169 also fall in this class.

[0019]

In the present invention, a pharmaceutically acceptable, solid organic acid such as citric, malic, maleic, fumaric or tartaric acid is used for pH adjusting purpose.

[0020]

3. Use of Pulsinecap™

[0021]

This method is disclosed by C.G.Wilson *et al.,* in Drug Delivery, 4:201-206 (1997).

[0022]

This colon targeted drug delivery system employs capsule bodies made of a water insoluble material such as low-density polyethylene and conventional gelatin capsule caps. The capsule body is filled with the drug in admixture with an excipient or carrier leaving an open space for placing a plug therein. Then a plug made of water-swellable hydrogels such as crosslinked polyethylene glycol is fitted in the opening to seal the capsule body at the neck thereof. Finally the gelatin cap is fitted over the capsule body and the seam is sealed with a suitable coating solution.

[0023]

On ingestion, the gelatin cap dissolves in the gastric juice and capsule body with exposed plug is allowed to pass from the stomach to the small intestin where the hydrogel plug expands in volume progressively by hydration. At a predetermined time point, the expanded plug is ejected from the neck of capsule body and the capsule content is released to the digestive tract. The time at which the plug is ejected may be controlled as desired by adjusting the dimension and the size thereof.

[0024]

4. Use of coating films or capsules made of biodegradable polymers

[0025]

It is known that the microorganism flora found in the

large intestine produces an enzyme which reduces and cleaves azo-linking groups. Accordingly, polymers containing azo-linking groups (azo polymers) are specifically degraded (depolymerized) in the large intestine. Based on this phenomenom, a colon-targeted DDS may be designed by coating tablets with the azo polymer or encapsulating a drug in a capsule made of the azo polymer.

[0026]

A variety of azo polymers have been known and a typical example thereof is styrene-hydroxyethyl methacrylate-divinyl azobenzene copolymer. Other colon-degradable polymers are known and include a polyester polymer which is co-polyester of terephthalic acid with cellobiose and polytetramethylene glycol (CTPT polymer) published by Takada *et al.,* in Pham. Tech Japan, Vol. 11(11), 37(1995).

[0027]

5. Use of time-controlled, colon-targeted delivery capsules

[0028]

This system is disclosed in U.S. Patent No. 5,637,319 to Kanji Takada. Briefly, the system utilizes capsules made of ethylcellulose. The capsule contains the drug and a water swellable substance. When administered, the capsule ruptures after elapsing a time at which sufficient force is exerted on the capsule wall to rupture the capsule and

release the drug as the water swellable substance swells.

[0029]

Examples of water swellable substances include low substitution-degree hydroxypropylcellulose, CMC sodium and CMC calcium. The swellable substance is compressed into a suitable shape such as tablet that fits within the capsule at a suitable location. The drug, glycyrrhizin in this case, is placed as a mixture with a pharmaceutical excipient or carrier in the remaining space within the capsule. A number of microholes are defined through the capsule wall in the area facing the shaped swellable substance. Except these microholes, the capsule is sealed.

[0030]

When administered orally, water will enter inside the capsule through the microholes and swell the swellable substance to exert a pressure on the capsule wall for a time until the contained drug is released by the rupture of the capsule. The rupturing time of the capsule may be controlled for the colon targeted delivery by adequately selecting the number and diameter of microholes, the capsule wall thickness, the type and size of water swellable substance.

[0031]

6. Use of Internal pressure-collapsible, colon-targeted delivery capsules

[0032]

This system is also disclosed in U.S. Patent No. 5,637,319 to Takada and Seizai-to-Kikai (Pharmaceutical preparations and machines), January 15, 1998 issue.

[0033]

This capsule is collapsed in the colon as follows. Ingested diet is flowable in the stomach and small intestine because of abundant presence of water-containing digestive juice whereas the content in the large intestine becomes highly viscous since reabsorption of water and formation of stool take place there. In such a dense environment, the capsule will rupture by the internal pressure associated with the peristalsis of colon to release the drug contained therein.

[0034]

The capsule is made of ethylcellulose or gelatin lined with ethylcellulose inside. Since the capsule content must be a liquid form when the capsule is collapsed, glycyrrhizin is contained in the capsule as a solution or dispersion in propylene glycol, polyethyleneglycol or vegetable oils, or dispersed in a base for making rectal suppositories which liquify at the body temperature. The rupture time in the colon may be controlled by varying the wall thickness of the ethylcellulose capsule.

[0035]

All patents, patent applications and publications cited

above are incorporated herein by reference.

[0036]

Indications of the glycylrrhizin preparation of the present invention include hepatic dysfunction in chronic hepatic disease, various eczema, drug rush, stomatitis, infant strophulus, phlyctena, alopecia areata and the like. The dose of the glycyrrhizin preparation of the present invention may be determined depending on the age, body weight, the type and severity of disease of a particular patient. The daily dose for adult patients (60kg of body weight) with chronic hepatic disease ranges between 10mg and 1,000mg, preferably between 100mg and 800mg as glycyrrhizin. This dose may be administered at once or divided twice or more.

[0037]

EXAMPLE

The invention will be described in detail by making reference to the following non-limiting examples.

[0038]

Example 1

100mg of glycyrrhizin sodium salt and 100mg of HCO-60 (polyoxyethylene hydrogenated castor oil) were dissolved in 0.5 ml of propylene glycol. A colon-targeted delivery capsule of the intra-colon pressure collapsible type (gelatin capsule having inner ethylcellulose lining) was produced by

filling the capsule with the above solution.

[0039]

Example 2

100mg of glycyrrhizin potassium salt was dispersed in 400mg of molten Witepsol™ H15 (higher fatty acid di- and triglyceride) heated at 50℃. The dispersion was poured into a mold and then cooled well to 6℃ to obtain a solid article having supository-like shape. This shaped article was dusted with fine talcum powder and then coated with ethylcellulose film by the dipping method to thereby obtain a intra-colon pressure collapsible, colon-targeted delivery capsule.

[0040]

Example 3

Pulsincap™ (available from Scherer DDS Ltd., UK) was filled with 100mg/capsule of glycyrrhizin.

[0041]

Example 4

A tablet containing 100mg of glycyrrhizin was produced by the conventional method. The tablet was coated with a colon-degradable CTPT polymer film to obtain colon-targeted DDS.

[0042]

<u>In vivo bioavailability test</u>

Method:

The test preparation was orally administered with 50ml of water to adult beagle dogs having been fasted overnight for 12 hours. After administration, 2ml of blood samples were collected periodically over 24 hours from the jugular vein and assayed for plasma glycyrrhizin levels using HPLC. Commercial glycylrrhizin tablets (Glycyron™) were used as a control drug. The dose was 100mg as glycyrrhizin.

[0043]

Results:

	Plasma glycyrrhizin level (μ g/ml) Time after administration (hr.)				
	1	2	3	4	5
Glycyron tab.	ND*	ND	ND	ND	ND
Preparation of Ex.2	ND	ND	0.7	4.8	5.9

	Plasma glycyrrhizin level (μ g/ml) Time after administration (hr.)			
	6	8	10	24
Glycyron tab.	ND	ND	ND	ND
Preparation of Ex.2	4.7	3.7	3.1	2.9

* Not detected.

[0044]

As shown in the above table, glycyrrhizin was not

detected in the plasma after oral administration of commercial glycyrrhizin tables. In contrast, when the colon-targeted DDS capsule of Example 2 was orally administered, the plasma glycyrrhizin level began to rise 3 hours after the administration, reached a peak in 4-5 hours and remained at a therapeutically effective level at least up to 24 hours after the administration.

CLAIMS:

1. A colon-targeted drug delivery system for oral administration comprising an amount of glycyrrhizin sufficient to release the same at a concentration overwhelming the rate of hydrolysis thereof by the intestinal flora in admixture with a pharmaceutically acceptable carrier.

2. The drug delivery system according to claim 1 wherein all or a portion of said carrier consists of an absorption promoter selected from the group consisting of an organic acid, a surfactant and a chelating agent.

3. The drug delivery system according to claim 1 or 2 wherein a suppository preparation containing glycyrrhizin is received in an anionic polymer capsule.

4. The drug delivery system according to claim 1 or 2 wherein glycyrrhizin is received together with an organic acid in a gelatin capsule having on the outer surface thereof a multi-layered coating consisting of a gastro-soluble film, a water-soluble film and an enteric film in the mentioned order.

5. The drug delivery system according to claim 1 or 2 wherein the system comprises a water-insoluble capsule body and a water soluble capsule cap, and wherein glycyrrhizin in a mixture with said carrier is placed in said capsule body inwardly from a hydrogel plug that closes the

opening the capsule body.

6. The drug delivery system according to claim 1 or 2 wherein a glycyrrhizin-containing tablet has been coated with a colon-soluble polymer.

7. The drug delivery system according to claim 1 or 2 wherein glycyrrhizin in admixture with said carrier is received in a capsule made of a colon-soluble polymer.

8. The drug delivery system according to claim 1 or 2 wherein the system comprises a capsule made of ethylcellulose defining a number of microholes in an area of the capsule wall and a shaped mass of a water-swellable substance facing the microholes, and wherein glycyrrhizin in admixture with said carrier is received in the remaining space of said capsule.

9. A method of enhancing the bioavailability of orally administered glycyrrhizin comprising providing a colon-targeted drug delivery system containing glycyrrhizin, orally administering said system to a human subject, and allowing the system to release glycyrrhizin selectively in the colon.

ABSTRACT

A drug delivery system for enhancing the bioavailability of glycyrrhizin is disclosed. The system is a colon-targeted, oral drug delivery system containing a sufficient amount of glycyrrhizin to overwhelm the rate of hydrolysis thereof by the intestinal flora in admixture with a pharmaceutically acceptable carrier. Preferably all or a part of the carrier consists of an adsorption promoter selected from the group consisting of a pharmaceutically acceptable organic acid, a surfactant and a chelating agent.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ORAL DRUG DELIVERY SYSTEM FOR ENHANCING THE BIOAVAILABILITY OF ACTIVE FORM OF GLYCYRRHIZIN

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/JP99/05153

on September 20, 1999,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowlege the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
JAPAN	286040/1998	September 21, 1998	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED *(if any)*			

POWER OF ATTORNEY: As a named inventor, I hereby appoint I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E. J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-King (33,302); Richard J. Traverso (30,595); Richard E. Kurtz (33,936); John A. Sopp (33,103) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
205	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
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	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY

Combined Declaration For Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
210	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
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	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	DATE	SIGNATURE OF INVENTOR 207	DATE
Kenji Tahada	Feb. 15, 2001		
SIGNATURE OF INVENTOR 202	DATE	SIGNATURE OF INVENTOR 208	DATE
SIGNATURE OF INVENTOR 203	DATE	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE